Australian Government

Department of Health

Application 1492

(Representing merged applications 1458 & 1461)

Non-Invasive Prenatal Testing (NIPT) for Common Trisomies (21, 18 and 13)

Ratified PICO Confirmation

(To guide a new application to MSAC)

(Version 0.1)

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Population 1: Primary testing

Component	Description
Patients	All pregnant women
Prior tests (for investigative medical services only)	None
Intervention	Non-invasive prenatal testing (NIPT) to assess the risk of fetal trisomies (specifically 21, 18 and 13) by detecting trophoblastic or fetal DNA circulating in maternal blood. Not limited to any specific product. Use of NIPT to additionally detect monosomy X will be considered as a sensitivity analysis.
Comparator	Combined first-trimester testing (CFTS) which includes: • Ultrasound for nuchal translucency (NT) at 11 to 13 completed weeks of pregnancy • Maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A))
Reference standard	Either genetic verification through amniocentesis, CVS, or fetal pathologic examination after abortion or birth, or postnatal phenotypic assessment

Outcomes	<u>Safety</u>
	
	<u>Efficacy/effectiveness</u>
	• Sensitivity/specificity/positive predictive value/negative predictive value/ROC area under the curve (AUC) for
	  ○ Trisomy 21
	  ○ Trisomy 13
	  ○ Trisomy 18
	  ○ Monosomy X
	• Rate of uninterpretable tests/ repeat tests required
	• Invasive procedures avoided (amniocentesis/CVS)
	• Change in number of genetic consultations
	• Quality of life (avoidance of anxiety)
	• Trisomy 21 cases detected/undetected
	• Trisomy 13, Trisomy 18 cases detected/undetected
	• Other chromosomal abnormalities detected/undetected (monosomy X, microdeletions)

Component	Description
	Healthcare resources • Cost of testing • Cost of counselling • Cost of first trimester ultrasound and maternal serum biomarker evaluation • Cost amniocentesis and CVS (including cost of the procedure and lab testing) • Cost of termination • Cost of Down syndrome birth Cost-effectiveness • Cost per true positive/trisomic fetus detected • Cost per non-trisomic fetus saved Total Australian Government Healthcare costs

Population 2: Contingency screening

Component	Description
Patients	Pregnant women at intermediate risk of fetal aneuploidy, defined as a risk of ≥1 in 300 following combined first trimester testing (CFTS) The intermediate risk threshold of ≥1 in 300 is to be used as a base case, with sensitivity analysis performed using different definitions of low, intermediate and high risk. This sensitivity analysis should include defining intermediate risk as between <1:1,000 to >1:10.
Prior tests (for investigative medical services only)	CFTS consisting of: • Ultrasound for nuchal translucency (NT) at 11 to 13 completed weeks of pregnancy • Maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A))
Intervention	Non-invasive prenatal testing (NIPT) to assess the risk of fetal trisomies (specifically 21, 18 and 13) by detecting trophoblastic or fetal DNA circulating in maternal blood. Plus prior tests (CFTS) NIPT is not limited to any specific product. Use of NIPT to additionally detect monosomy X will be considered as a sensitivity analysis.
Comparator	Prior tests (CFTS) alone (without NIPT)
Reference standard	Either genetic verification through amniocentesis, CVS, or fetal pathologic examination after abortion or birth, or postnatal phenotypic assessment
Outcomes	Safety

Component	Description

	Efficacy/effectiveness
	• Sensitivity/Specificity/positive predictive value/negative predictive value, ROC area under the curve (AUC) for
	  ○ Trisomy 21
	  ○ Trisomy 13
	  ○ Trisomy 18
	  ○ Monosomy X
	• Rate of uninterpretable tests/repeat tests required
	• Invasive procedures avoided (amniocentesis/CVS)
	• Change in number of genetic consultations
	• Quality of life (avoidance of anxiety)
	• Trisomy 21 cases detected/undetected
	• Trisomy 13, Trisomy 18 cases detected/undetected
	• Other chromosomal abnormalities detected/undetected (monosomy X, microdeletions)
	Healthcare resources
	• Cost of testing
	• Cost of counselling
	• Cost amniocentesis and CVS (including cost of the procedure and lab testing)
	• Cost of termination
	• Cost of Down syndrome birth
	Cost-effectiveness
	• Cost per true positive/trisomic fetus detected
	• Cost per non-trisomic fetus saved
	Total Australian Government Healthcare costs

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

Prenatal screening is a routine medical service for a pregnant woman to evaluate the risk of fetal aneuploidy. These aneuploidies include but are not limited to;

- trisomy 21 (Down syndrome),
- trisomy 18 (Edward syndrome),
- trisomy 13 (Patau syndrome).

Trisomies 21, 18 and 13 account for approximately 80% of major chromosome abnormalities detected prenatally.

Down syndrome is the most common chromosomal cause of intellectual disability in children and adults, occurring with a frequency in the population of approximately 1 in 800. Maternal age is the most important risk factor for having a child with trisomy 21; approximately 1 in 300 for a maternal age of 35 years and 1 in 100 when aged 40 years. Australia, in common with other developed countries, has an increasing frequency

of children born to mothers in these age groups with a corresponding increase in the prevalence of trisomy 21.[1]

Edwards syndrome occurs in approximately 1 in 5,000 newborns causing intrauterine growth retardation, low birth weight and multiple life-threatening physical abnormalities so that only 5-10% of affected children survive beyond one year of age.[2]

Patau syndrome occurs in approximately 1 in 16,000 newborns usually causing severe intellectual disability and life-threatening physical abnormalities so that only 5-10% of affected children survive beyond one year of age. The risk of trisomy 13 increases with maternal age.[2]

Two patient populations are considered:

1: Primary testing – all pregnant women

All pregnant women are at risk of fetal aneuploidy, and therefore the first population is to test all women who are pregnant. Currently in Australia this is approximately 300,000 women per year.

2. Contingency screening – women at intermediate risk of having a child with a fetal aneuploidy

Pregnant women at intermediate risk of fetal aneuploidy are identified using the current prenatal testing approach and are subsequently offered NIPT.

As a base case, intermediate risk of fetal aneuploidy is considered to be a risk of ≥1 in 300 and is calculated from factors including but not limited to:

- Maternal age equal to or greater than 35 years
- Abnormal maternal serum or ultrasound nuchal translucency results
- Family history of chromosomal abnormalities.

It is estimated that the number of pregnant women in population 2 would be approximately 66,000 (i.e. the number of pregnant women aged >35 years).

The risk cut-offs used to define low, intermediate and high risk would be explored as part of the assessment. The low risk threshold could eventually be reduced to a level where all women are offered NIPT, irrespective of the CFTS risk assessment, thereby negating the utility of CFTS as a triage tool for the detection of common trisomies prior to NIPT.

Rationale

Existing non-invasive prenatal testing for fetal aneuploidy consists of combined first trimester testing (CFTS) at 11^{+0} and 13^{+6} weeks of pregnancy by calculating the overall risk for trisomy 21 from:

- maternal age,
- ultrasound measurement of fetal nuchal translucency (NT) and
- maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)).

While no one of these tests has sufficient sensitivity and specificity on its own, as a combination, recommended performance standards for screening are achieved with a sensitivity of 85%, specificity of 95% and a positive predictive value of approximately 7 to 10%.[1] Risk results for trisomy 13 and 18 can also be incorporated into the first trimester combined screening algorithm.[1]

Currently approximately 80% of pregnant women in Australia receive first trimester antenatal care. However, for those who do not attend a medical practitioner until later in pregnancy, alternative screening is required.

Second trimester screening consists of a maternal serum biochemical quadruple test (alpha-fetoprotein (AFP), β-hCG, unconjugated oestriol, and inhibin A). This screening for trisomy 21 is reported to have a sensitivity of 75%, specificity of 95% and a positive predictive value of approximately 2 to 3%. [1] An ultrasound at 18-20 weeks of pregnancy is not recommended as a primary screening test for trisomy 21 due to its relatively poor sensitivity and specificity.[1]

Secondary confirmatory genetic testing is required where high risk is identified. This is undertaken on samples obtained from the fetus using invasive techniques; amniocentesis or chorionic villus sampling (CVS) for fetal karyotyping.

Amniocentesis at 14-20 weeks gestation has a 1% higher risk of fetal loss and is associated with an increased risk of respiratory distress syndrome and pneumonia.[3] Amniocentesis at 10-14 weeks gestation has 2% higher risk of fetal loss and has a 1.6% higher risk of talipes equinovarus (club foot) than first-trimester CVS or second trimester amniocentesis.[3]

First trimester CVS has a similar risk to second trimester amniocentesis. However CVS must be performed after 10 weeks gestation to avoid other fetal abnormalities (fetal transverse limb abnormalities, micrognathia and microglossia).[3]

The rationale for patient population 1 (all pregnant women) is that it would increase the detection of fetal aneuploidy with a corresponding reduction in invasive testing, which would reduce iatrogenic euploid losses.

The rationale for patient population 2 (contingency screening) is that it would maintain the current rate of detection of fetal aneuploidy with a corresponding reduction in invasive testing, which would reduce iatrogenic euploid losses. The applicant indicates this would include detection of non-T21/18/13 abnormalities, which are enriched in patients at high risk on the cFTS e.g. Norton et al Obstet and Gynecol 2014, 124(5):979-986; Norton et al Am J Obstet Gynecol 2016;214:727.e1-6; Petersen et al, Ultrasound Obstet Gynecol 2014, 43(3):265-71. The applicant also indicates Vogel et al, Ultrasound Obstet Gynecol 2017 (Epub) presents data suggesting a 'cut-off' for invasive testing by microarray (rather than NIPT) might reasonably be set as high as 1/300, as multiple other aneuploidies/pathogenic CNVs were detected in patients in this risk group who underwent array testing.

Population 2 provides a cheaper option than patient population 1. The criteria for contingency screening and categorisation of 'intermediate risk' (≥1 in 300) are based on current practice for CFTS and define the population currently recommended for invasive testing. Other options for defining this population should be considered (for example, an intermediate risk threshold defined as between <1:1,000 and >1:10).

Turner syndrome (monosomy X) does not cause intellectual disability but affects physical development and ovarian function. A proportion of affected individuals have heart defects, skeletal abnormalities and renal impairment. Turner syndrome occurs in approximately 1 in 2,500 newborn girls worldwide and the risk for Turner syndrome does not increase with maternal age. NIPT is sometimes also used to detect monosomy X. PASC advised that the detection of monosomy X should be considered as a sensitivity analysis to consider the further incremental costs and outcomes of identifying monosomy X. If evidence is available, this could include additional options for identifying other aneuploidies and micro deletions beyond monosomy X.

Prior tests

1: Primary testing – all pregnant women

No prior tests. All pregnant women are eligible.

2. Contingency screening – women at increased risk of having a child with a fetal aneuploidy

The prior tests are combined first trimester testing (CFTS) at 11^{+0} to 13^{+6} weeks of pregnancy which includes:

- ultrasound measurement of fetal nuchal translucency (NT) and
- maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)).

Note these prior tests are only applicable for women who present to a medical practitioner in the first trimester of pregnancy. For women who present later in pregnancy, the following prior test would be undertaken:

- serum biochemical quadruple test (alpha-fetoprotein (AFP), β-hCG, unconjugated oestriol, and inhibin A).

Intervention

Non-invasive prenatal testing through the analysis of cell free fetal DNA is a major technological advancement in testing for fetal aneuploidy.

Until recently, obtaining tissue of fetal origin for genetic testing could only be obtained by invasive techniques such as amniocentesis (amniotic fluid samples containing fetal cells mostly of epithelial origin) or chorionic villus sampling (placental samples containing mesodermal connective tissue and trophoblastic cells of the placenta). However DNA from the fetus is found circulating in maternal blood in intact fetal cells or after the breakdown of cells (mostly placental) as cell free DNA. Only 10-15% of cell free DNA circulating in maternal blood is fetal in origin but this fetal fraction can now be detected and measured.

In NIPT, cell free fetal DNA (cffDNA) is analysed to detect quantitative differences in the number of DNA fragments of different chromosomes to distinguish fetal aneuploidies from unaffected pregnancies.

The test requires a venepuncture to be performed on the pregnant woman for the collection of a blood sample that is referred to a pathology laboratory for genetic analysis. Testing would be provided by Approved Practising Pathologists in line with other tests in the MBS Pathology Table.

NIPT would be offered as part of routine clinical care and provided after 10 weeks gestation. It would be offered once per pregnancy, unless a repeat test was required due to test failure (estimated 1.6% [4]). The applicant stated this is assay dependent and may range from 1.5% to 6%, depending on the test. The NIPT can be offered, and the referral made, by an obstetric specialist, midwife or GP. NIPT testing should be performed by a NATA accredited pathology laboratory. NIPT requires two cfDNA collection tubes. These are similar to standard blood collection tubes, but with a solution to prevent cell lysis (breakdown), thereby improving the yield of fetal cfDNA.

The NIPT result would be reported to the treating medical practitioner or midwife, who would advise the patient of the result and provide counselling where required. Human nucleic acid tests can only be requested by medical practitioners (i.e. doctors), in line with S1.1 of the NPAAC Human Nucleic Acid testing requirements). However, a midwife requesting on behalf of an obstetrician with clinical responsibility for

the patient's care is acceptable. Additional training and expertise may be required for counselling linked to use of NIPT, as it has a higher positive predictive value than CFTS.

Various assays are available for NIPT using the same scientific principles. The assessment will consider all commercial products and would allow for the use of any product which has regulatory approval on the Australian market. It is anticipated that new products will continue to be developed using the same scientific principles.

cfDNA is a highly variable analyte [5-7]. In non-pregnant subjects, the concentration of cfDNA rises 10-fold with exercise, inflammation or obesity and can return to baseline levels within 90 minutes. In a pregnant woman, such a rise would reduce the corresponding proportion of cfDNA derived from the fetus and render assessment of fetal aneuploidy impossible. In the presence of sufficient fetal cfDNA for analysis, NIPT is highly sensitive and specific. Given the importance of fetal fraction to test performance, explicit criteria for the measurement of fetal fraction may be required in the MBS item descriptor.

NIPT is not currently subsidised in Australia by Government or private health insurance. Women may self-fund the test. The RANZCOG considers that this financial barrier poses major ethical and economic challenges to the successful incorporation of NIPT testing into prenatal care and precludes them from providing universal recommendations.

Rationale

This PICO confirmation states that NIPT is used to test for common fetal aneuploidies, trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome). The same aneuploidies are tested for under the current CFTS.

The submission by the Royal Australian College of General Practitioners (RACGP) raises the concern regarding the use of NIPT for screening for sex chromosome aneuploidies and microdeletions on the basis that:

- The positive predictive values (PPVs) for sex chromosome aneuploidies and microdeletions are low (if known)
- They are unlikely to be reported in the test results
- Therefore decision-making will be based on low-quality information, and these decisions may include non-medical sex selection
- The testing laboratories may add an additional charge for these results.

More broadly, the RACGP requests PPVs for each condition be clearly stated, both in marketing materials and when laboratory results are reported, in order to assist in decision making. It will be difficult, however, to ensure laboratories follow this practice. The applicant states it is not possible to determine patient-specific post-test risks without information the laboratory often does not have. 'PPV' calculated from a large population of patients may be very different to post-test risk for an individual.

Given that this application is for any NIPT product with regulatory approval on the Australian market, and with the knowledge that the technology will continue to evolve, consideration should be given as to how additional information provided by the test may be used, particularly information on sex chromosomes and any other information which may be able to be provided as the technology changes. This should include consideration of potential ethical issues and analysis of consumer preferences, both pregnant women and their partners and the broader community.

Comparator

1: Primary testing – all pregnant women

The comparator tests are combined first trimester testing (CFTS) at 11^{+0} to 13^{+6} weeks of pregnancy which includes:

- ultrasound measurement of fetal nuchal translucency (NT) and
- maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)).

Note these tests are only applicable for women who present to a medical practitioner in the first trimester of pregnancy. For women who present later in pregnancy, the comparator test would be second trimester maternal serum screening (2TMSS) which is undertaken between 14 and 20 weeks of pregnancy:

- serum biochemical quadruple test (alpha-fetoprotein (AFP), β-hCG, unconjugated oestriol, and inhibin A).

NIPT is a replacement test for CFTS and 2TMSS for the purpose of detecting common trisomies.

However, NIPT would not replace current combined FTS, but would be additional to current NT ultrasound and/or FTS biochemistry which would be used to detect conditions other than fetal trisomies 21, 18 and 13. First trimester biochemistry may still be of use to determine the risk for other obstetric conditions; PaPP-A levels, for example, can help to determine the risk of fetal loss, preterm birth, intrauterine growth restriction and pre-eclampsia, and the detection of aneuploidies other than trisomies 21, 18 and 13 (outside the scope of this application for NIPT). Ultrasound is still advised for correct dating, diagnosis of multiple pregnancies, and chorionicity and anatomy assessment (fetal anomalies and physical deformities).

2. Contingency screening – women at increased risk of having a child with a fetal aneuploidy

The comparator tests are CFTS followed by invasive testing (amniocentesis or CVS) in high risk women (risk greater than 1 in 300) (i.e. prior testing alone). The applicant states that Vogel et al 2017 (cited above) provides recent analysis on implications of a 1/300 'cutoff'

In this population, NIPT is used as a triage test to reduce the use of invasive testing in high-risk women. It is expected that NIPT will better target use of amniocentesis and CVS thus reducing, but not eliminating, their use.

Rationale

The accuracy of NT ultrasound measurement is highly operator dependent. Operator training and expertise are critical and access to specialised operators maybe variable across the country.

Outcomes

Patient relevant

No specific safety outcomes are listed. NIPT is considered a safe test as it only requires collection of maternal blood, a routine procedure during pregnancy.

1: Primary testing – all pregnant women

The introduction of NIPT is expected to increase the detection of fetal aneuploidies and reduce utilisation of invasive testing (amniocentesis and CVS), which would reduce iatrogenic euploid losses from these tests. Therefore the key patient-relevant health outcomes are:

- trisomy cases detected
- invasive procedures avoided.

2. Contingency screening – women at increased risk of having a child with a fetal aneuploidy

The introduction of NIPT is expected to maintain the current rate of detection of fetal aneuploidies and reduce utilisation of invasive testing (amniocentesis and CVS), which would reduce iatrogenic euploid losses from these tests. Therefore the patient-relevant outcomes are the same as for primary testing using NIPT.

Healthcare system

The introduction of NIPT is not expected to reduce the use of first trimester ultrasound.

The introduction of NIPT using either scenario is expected to reduce the use of invasive testing. If NIPT were used for primary screening then its introduction would also be expected to reduce the number of births of babies with trisomies which would affect healthcare resources.

It is not clear what impact either scenario would have on the utilisation of counselling services for pregnant women undergoing screening.

Rationale

Diagnostic performance is not a patient relevant outcome but is critical for understanding how the test compares to existing prenatal screening and diagnosis and how clinical practice may change were the test publicly funded.

Additional outcomes for both scenarios are listed in the summary of the PPICO. It is important to report, where possible, the actual changes that occur rather than modelled changes based on test performance. For example, a positive NIPT would prompt a woman to be offered an invasive test but not all women will take up this offer, furthermore, some women who have a negative NIPT or do not undergo NIPT, may still elect to have an invasive test.

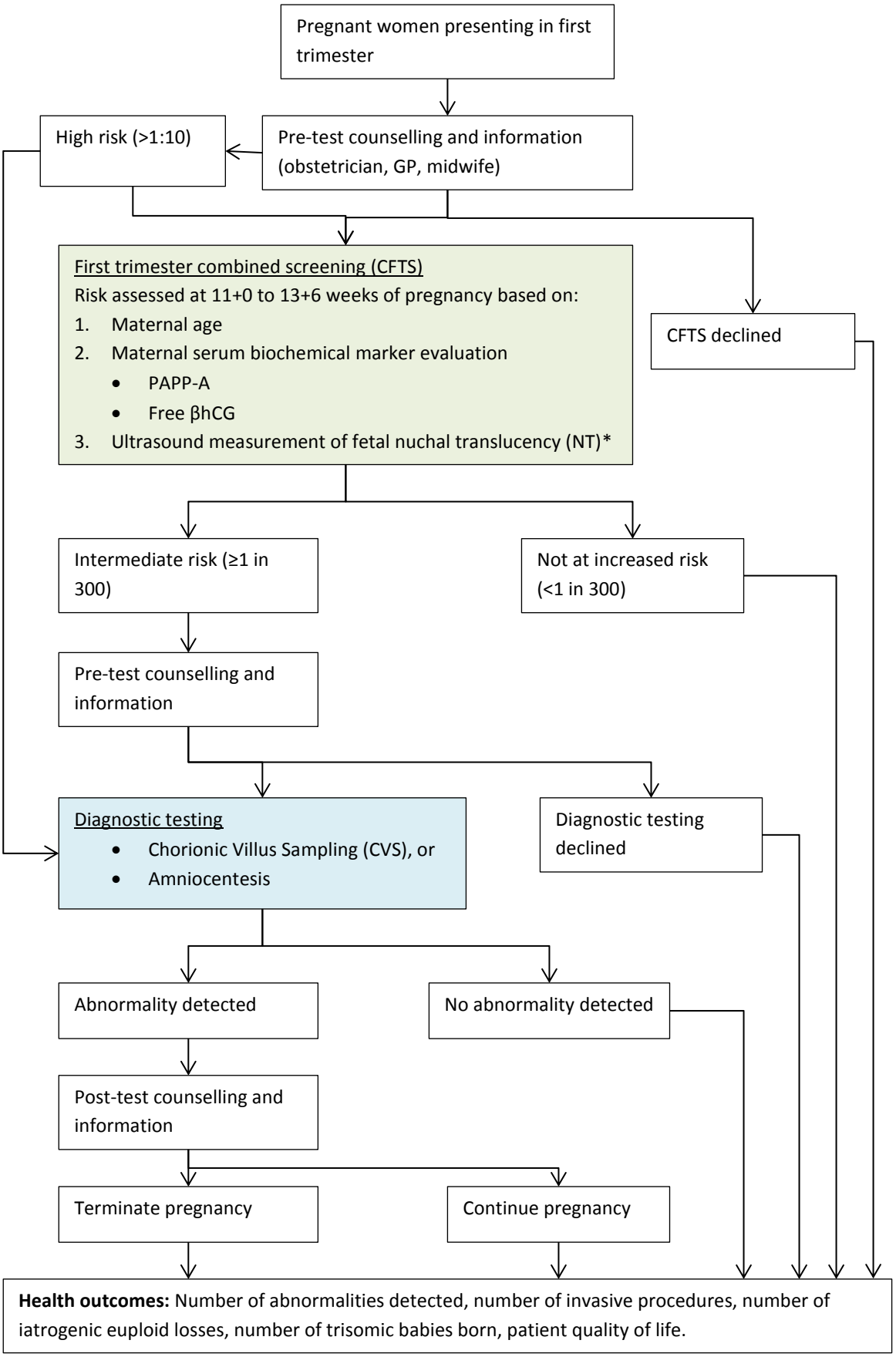
The importance of the outcomes listed in the PPICO may depend on the perspective taken, for example, the most patient relevant outcomes are likely around pregnant women's quality of care experiences (captured as quality of life in the outcomes table) which may include access to, and ability to understand, information relating to screening and the testing options available, levels of anxiety and participation in decision making.

As discussed, NIPT is a technology which can already detect many more conditions than those considered in this application. The test characteristics of some of these (sex chromosome aneuploidies, microdeletions) are requested as outcomes in the PPICO. The applicant notes the contingent model will detect abnormalities which cannot be detected by NIPT. Detection of additional conditions through the test will change overall rates of false positives, utilisation of downstream services (diagnostic testing and counselling) and overall economics of the test. The extent to which there will be available data to address these issues (and model their impact) is unclear. It is also unclear how this will be best incorporated into the assessment.

A case could also be made that this is an application for which consideration of ethical and societal implications of the technology should be considered and prioritised in the assessment.

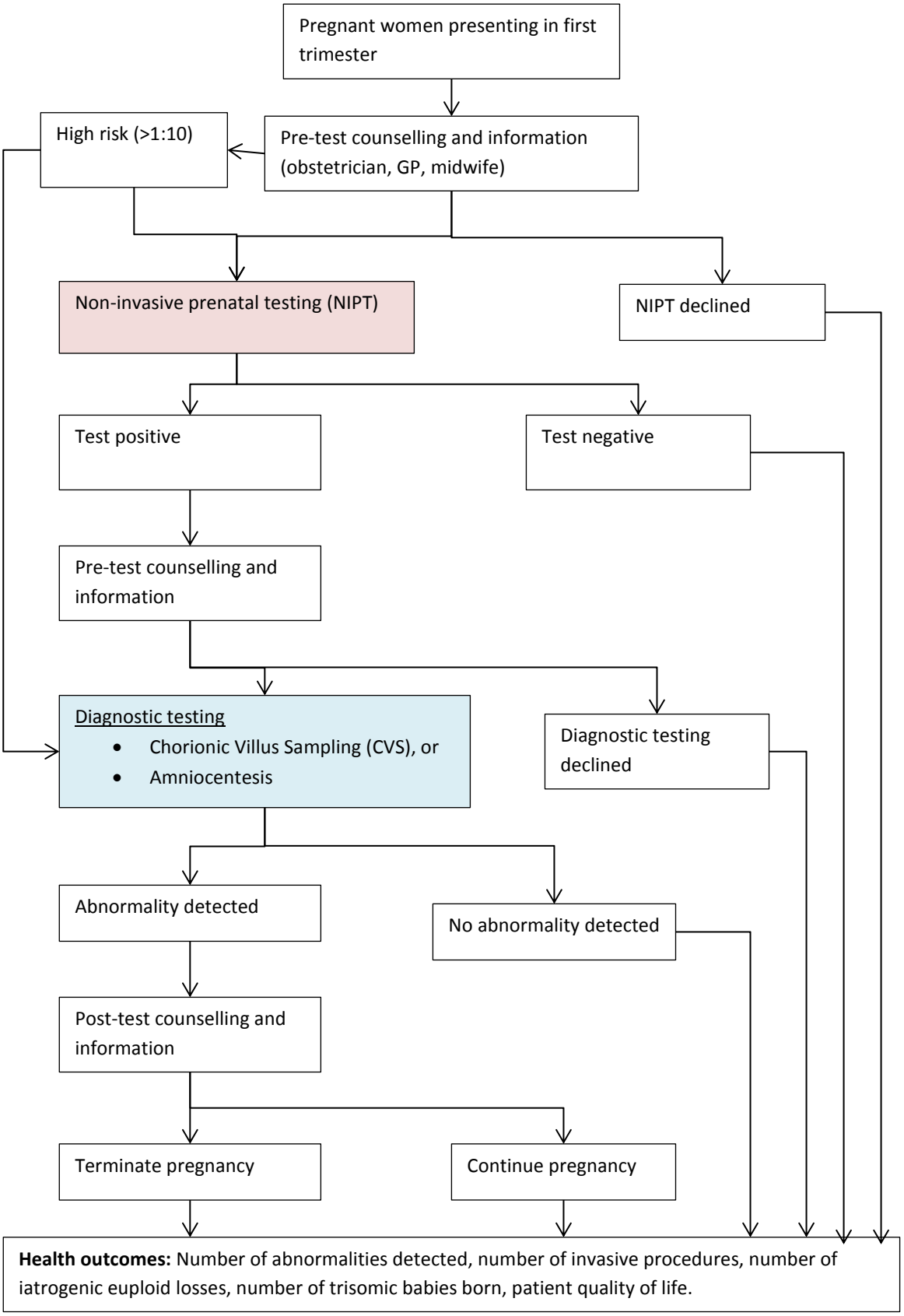
PASC noted the evaluation of NIPT would benefit from the approach and outcomes outlined in the Clinical Utility Card proforma (available from http://www.msac.gov.au/internet/msac/publishing.nsf/Content/applicants)

Current clinical management algorithm for pregnant women presenting in first trimester

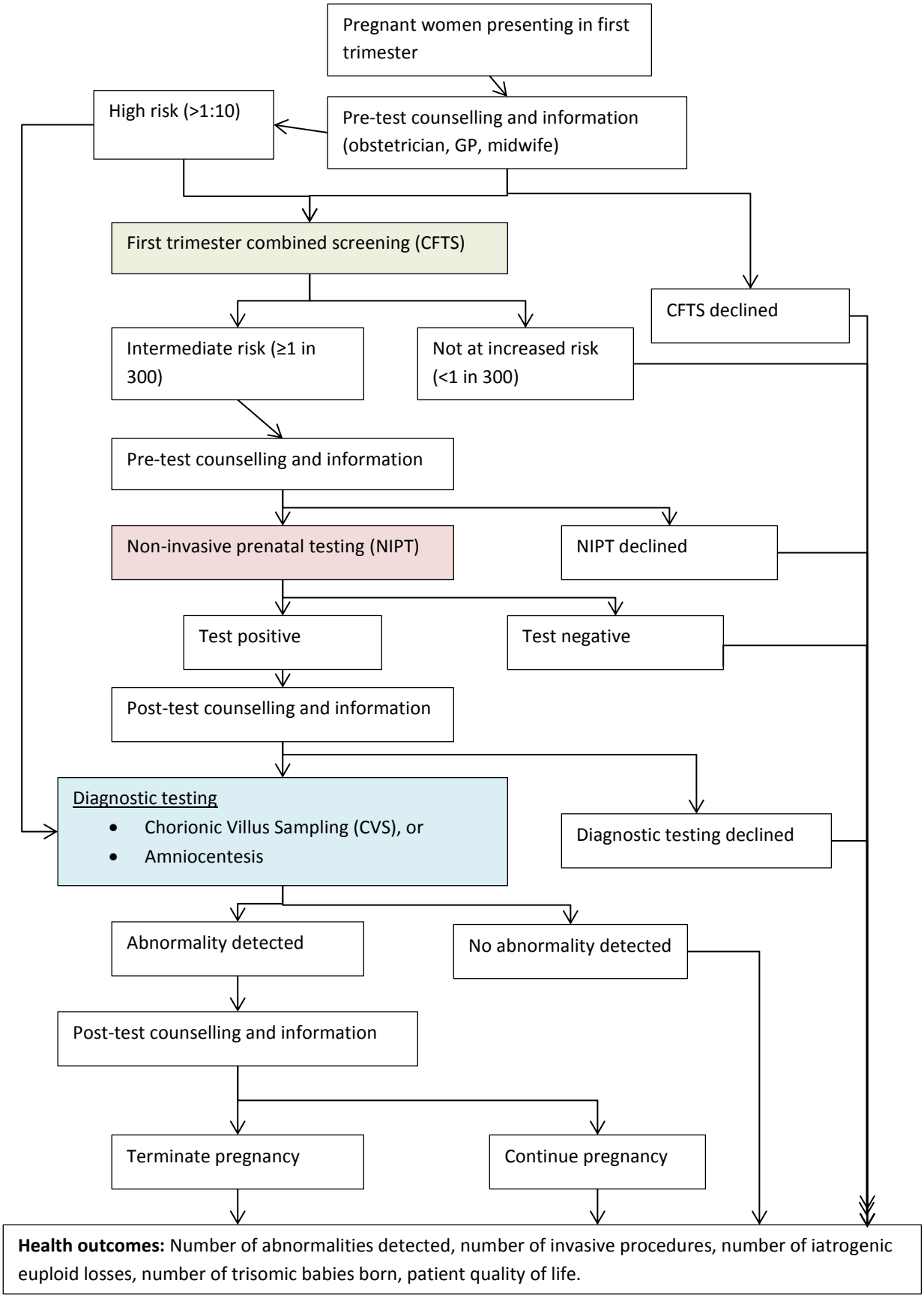


Notes: * Rural and remote women may not have access to local ultrasound NT measurement. These women may choose to travel to access services, to have risk assessed based on age and maternal serum biochemical markers only, to have risk assessed based on age and both first and second trimester maternal serum biochemical markers or they may decline or not be offered prenatal screening [8].

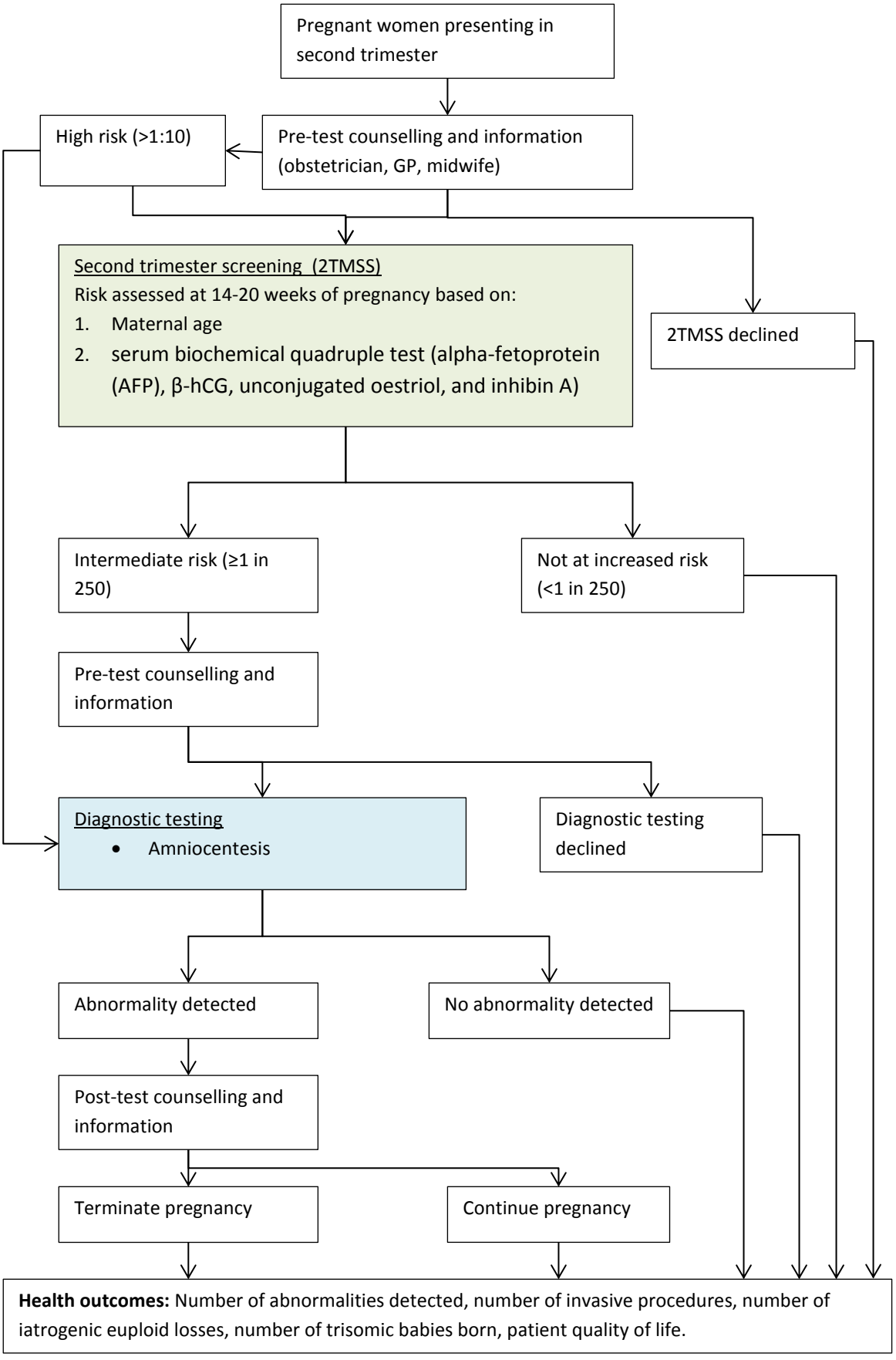
Proposed clinical management algorithm for pregnant women presenting in first trimester – primary screening



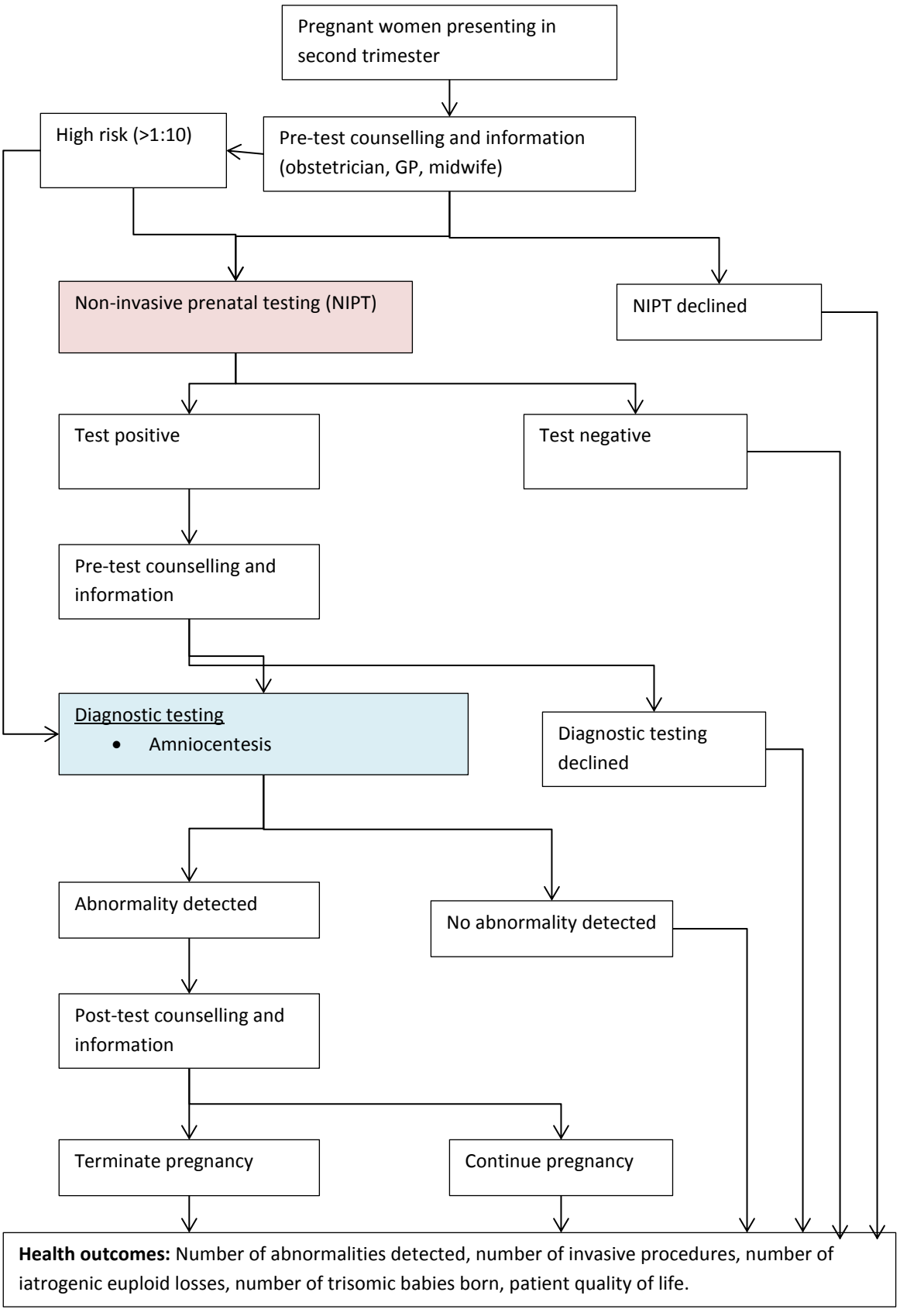
Proposed clinical management algorithm for pregnant women presenting in first trimester – contingency screening



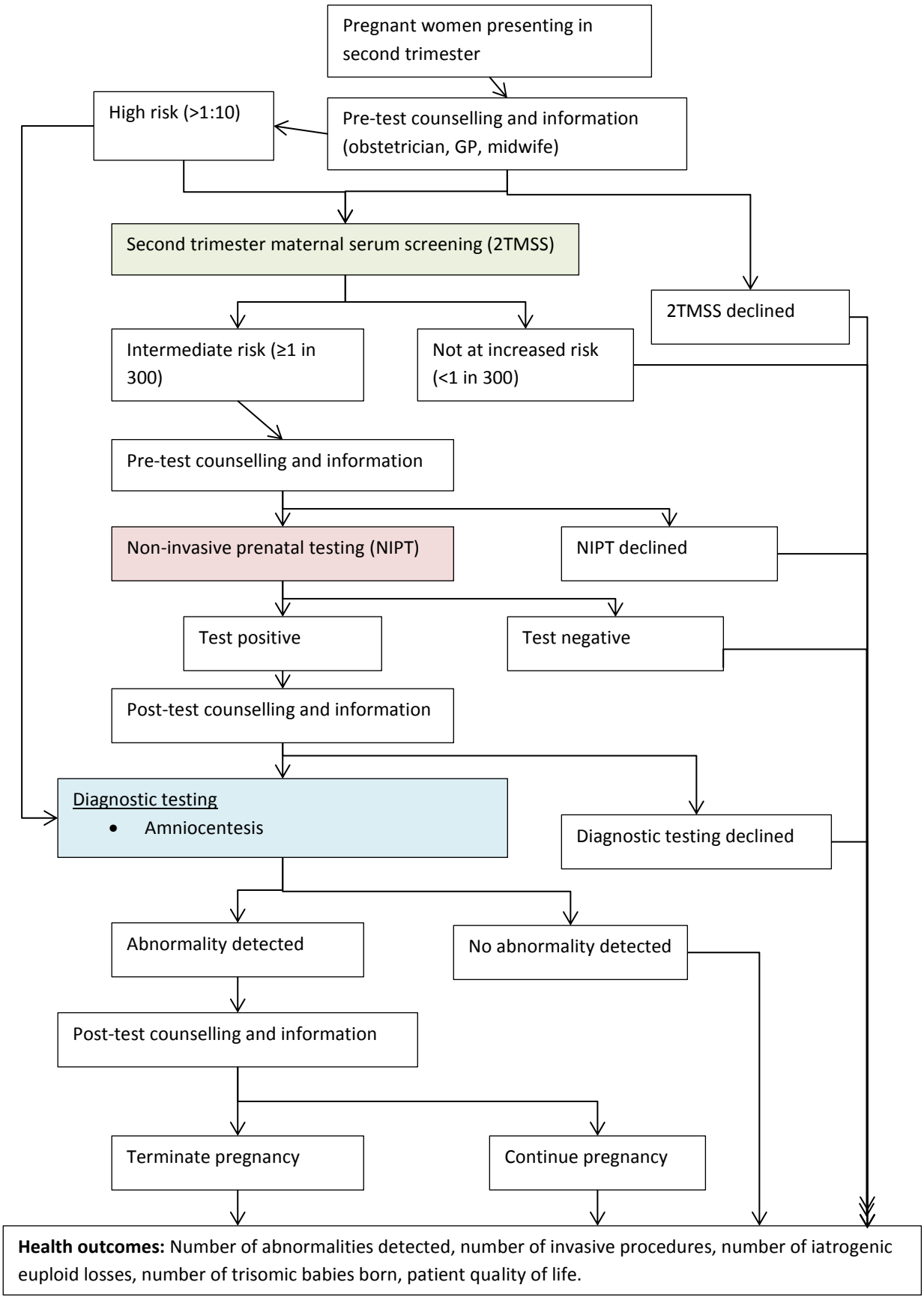
Current clinical management algorithm for pregnant women presenting in second trimester



Proposed clinical management algorithm for pregnant women presenting in second trimester – primary screening



Proposed clinical management algorithm for pregnant women presenting in second trimester – contingency screening



Proposed economic evaluation

The clinical claim is that NIPT is non-inferior in safety and superior in clinical effectiveness to current testing. According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative* the required economic analysis is therefore a cost-utility analysis. However, a cost-consequences analysis would in this assessment be considered helpful and may provide more useful information to the decision maker than aggregated utility values.

Proposed item descriptor

The following item descriptor is proposed if NIPT were publicly funded for primary testing.

Category 6 (Group P7 Genetics) – Pathology services
Non-invasive Prenatal Testing of blood from a pregnant woman for the detection of the more common fetal aneuploidies; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome) in trophoblastic or fetal DNA circulating in maternal blood. Fee: $500

The following item descriptor is proposed if NIPT were publicly funded for contingency screening.

Category 6 (Group P7 Genetics) – Pathology services
Non-invasive Prenatal Testing of blood from a pregnant woman at high risk for the detection of the more common fetal aneuploidies; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome) in trophoblastic or fetal DNA circulating in maternal blood. High risk pregnancy defined as a risk of ≥1 in 300 for fetal aneuploidy, calculated from factors including but not limited to: • maternal age of 35 years or greater • abnormal maternal serum markers • abnormal first trimester ultrasound nuchal translucency Fee: $500

PASC has advised that further consideration be given to any inclusion of "fetal fraction" in the MBS item descriptor as this would exclude some test options, different laboratories may have different cut points (e.g. a fetal fraction of 4%) for identifying anomalies, and this level of detail may be better addressed in a quality assurance program.

References

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